

RENIN, ANTIDIURETIC HORMONE AND THE KIDNEY IN WATER RESTRICTION AND REHYDRATION

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SUMMARY

1. The effect of restricted water intake followed by voluntary rehydration with water or 10 mM-KCl was studied in four conscious sheep with respect to plasma concentrations of renin, antidiuretic hormone (ADH), protein and electrolytes, and urine flow rate, osmolality and osmolal excretion.
2. Water restriction increased the plasma renin concentration and the plasma ADH concentration.
3. Rehydration with water caused a further rise in plasma renin, but plasma ADH returned to basal levels in less than 2 hr.
4. Rehydration with 10 mM-KCl in order to stabilize plasma K concentration greatly attenuated the post-drinking rise in plasma renin concentration, while plasma ADH levels fell as before.
5. Urine flow rates after rehydration with water and 10 mM-KCl remained low for at least 6 hr in most experiments despite low plasma ADH levels. The effect on urine osmolality ranged from no change to a large drop.
6. The post-drinking antidiuresis was associated with a reduction in solute excretion rate. However, free water clearance usually remained negative.
7. These experiments do not support the existence of a direct nexus between plasma ADH levels and plasma renin concentration.

INTRODUCTION

Dehydration of sheep by restriction of water intake increases plasma renin concentration, and rehydration by voluntary consumption of water causes a further three-to fourfold rise during the ensuing 12 hr (Blair-West, Brook & Simpson, 1972). Other unexpected features of the response to rehydration were almost total renal retention of Na, and urine flow rates that remained low for at least 12 hr. We suggested that the rise in plasma renin after rehydration might be due to reduced delivery of Na to, and its transport at, the macula densa in accordance with the mechanisms of renin release proposed by Vander (1967), Nash, Rostorfer, Bailie, Wathen & Schneider (1968) and Vander & Carlson (1969). Later experiments (Blair-

West, Brook & Simpson, 1977) in which dehydrated sheep drank NaCl solutions to correct their water deficit supported this suggestion.

The cause of the persistent antidiuresis after rehydration remained unexplained. Bonjour & Malvin (1970) and Malvin (1971) have claimed that high renin levels stimulate antidiuretic hormone (ADH) release. If this is so, the raised renin concentration after rehydration may have prevented plasma ADH levels from falling despite low plasma osmolality and an expanding extracellular fluid volume. Some recent findings give support to the existence of this mechanism (Uhlich, Weber, Eigler & Gröschel-Stewart, 1975; Claybaugh 1976), other findings give qualified or indirect support (Andersson & Westbye, 1970; Shimizu, Share & Claybaugh, 1973; Mouw, Bonjour, Malvin & Vander, 1971) and some findings are opposed to it (Claybaugh & Share, 1972; Share, Claybaugh, Hatch, Johnson, Lee, Muirhead & Shaw, 1972). There is also evidence (Bunag, Page & McCubbin, 1967; Vander, 1968; Gutman & Benzakein, 1971; Hesse & Nielsen, 1977) that renin release is suppressed by i.v. infusion of ADH, even at rates that may be deemed physiological (Travis & Share, 1971). Thus there may be a negative feed-back mechanism between sites controlling ADH release and the juxtaglomerular cells of the kidney.

These putative mechanisms raise the possibility that the rise of plasma renin concentration after rehydration may have stimulated ADH release and thus maintained the antidiuresis. Alternatively, if plasma ADH levels fall shortly after rehydration, the rise in renin concentration may have been caused by reduction of ADH inhibition of renin release.

These possibilities were tested by measuring ADH changes in thirsted sheep after rehydration by voluntary intake of water. In a second series of experiments, sheep were rehydrated by voluntary intake of 10 mM-KCl solution (with additions of small volumes of 1 M-KCl into the rumen in some experiments) in order to avoid the reduction of plasma [K] that is associated with plasma volume expansion after rehydration (Blair-West *et al.* 1972, 1977).

METHODS

Animals. Four adult Merino ewes weighing 32–43 kg were used. They were housed in individual metabolism cages with free access to water except during periods of water restriction. They were fed once daily 0.6–1.2 kg of an equal mixture of lucerne and wheaten chaffs. Urine was collected directly into a beaker from a condom glued around the vulva, the animals having been trained to urinate when touched gently on the hindquarters. Urinary flow and excretion rates were calculated from 1 hr urine collections except for the first two after drinking which were 45 min collections. At a previous operation permanent adhesions had been produced between a small area of rumen wall and skin on the left side in the region between the tuber coxae and the last rib. This allowed for easy cannulation of the rumen by needle puncture under local anaesthesia and the administration of fluids directly into the rumen.

Blood sampling. Control blood samples were taken by venepuncture on the day preceding the first day of water restriction. All other blood samples were collected through an indwelling catheter which had been inserted into a jugular vein on the day before the rehydration experiment. About 25 ml blood was taken at each sampling period into a syringe containing heparin and this volume was replaced with Haemaccel (Behringwerke A.G., Marburg). The blood was transferred at once to plastic centrifuge tubes immersed in ice. The blood was centrifuged at 10,000 rev/min for 20 min at -3°C . Part of the plasma was used to determine specific gravity

and Na and K concentrations; the remainder was stored at -20°C for plasma ADH and renin assays.

Analytical techniques. Plasma renin concentration was determined by an enzyme kinetic method (Blair-West, Coghlan, Denton, Scoggins, Wintour & Wright, 1967), and the results are expressed as ng angiotensin produced/hr per ml. of plasma. ADH in plasma was determined by radioimmunoassay after extraction (Pullan, Dax, Johnston & Burger, 1977). Na and K in plasma and urine were determined by flame photometry with an Auto Analyser (Technicon Instruments Corp. New York). Total protein in plasma was estimated by the copper sulphate specific gravity method (Varley, 1962). Urine osmolality was measured by freezing point depression with an Advanced Osmometer (Advanced Instruments, Inc.). Mean values are quoted as mean \pm s.e.m. of mean. Statistical analysis was done by 'paired *t* test' unless otherwise indicated.

Experimental. The animals' water intake was restricted for 8–15 days with the aim of producing a minimum body weight loss of 10% while the sheep continued to eat their daily ration of food. Thus the weight loss reflected largely a loss of body water. This was achieved by frequently weighing the animals and adjusting their water intake to between 250 and 750 ml./day. No attempt was made to reproduce the same degree of water depletion in each animal in each experiment. The experiments were divided into two groups, (i) rehydration with water and (ii) rehydration by administration of KCl solution to stabilize plasma [K]. On the day of the experiment the sheep were offered to drink, at body temperature, either water (four sheep, each one experiment) with resulting fall in plasma [K], or 10 mM-KCl (four sheep, each two experiments) which tended to stabilize plasma [K]. The water or KCl solution was removed after 2 hr. The animals always drank within 5 min most of the volume they ultimately consumed. In one early KCl experiment, plasma [K] 6 hr after drinking fell below control values. Therefore, in four of the KCl experiments more KCl was added directly to the rumen over a period of 80 min beginning 4.5 hr after drinking. In two experiments (sheep 86 and 95), 50 m-mole was added in five evenly spaced doses of 10 ml. 1 M-KCl. In the other two experiments (sheep 47 and 532) 100 m-mole KCl was similarly added in 20 ml. doses of 1 M-KCl.

RESULTS

The volumes of water and 10 mM-KCl drunk, the amounts of K imbibed and the weight losses incurred after varying regimens of water restriction are shown in Table 1.

TABLE 1. Quantities of water or 10 mM-KCl drunk and amounts of K imbibed after periods of water restriction, as well as weight losses incurred during water restriction

Liquid	Sheep no.	Vol. drunk (l.)	K intake (m-mole)	Weight loss (kg)
Water	47	6.30	—	4.0
	86	3.68	—	3.0
	95	6.75	—	4.5
	532	3.05	—	2.8
KCl (10 mM)	47	5.90	59.0	8.0
		5.03*	50.3	9.2
	86	4.61	46.1	3.6
		5.74*	57.4	5.1
	95	6.72	67.2	3.5
		6.51*	65.1	5.6
	532	4.25	42.5	3.9
		6.05*	60.5	5.3

* Additional KCl added to rumen between 4 hr 15 min and 5 hr 35 min after drinking (see Methods).

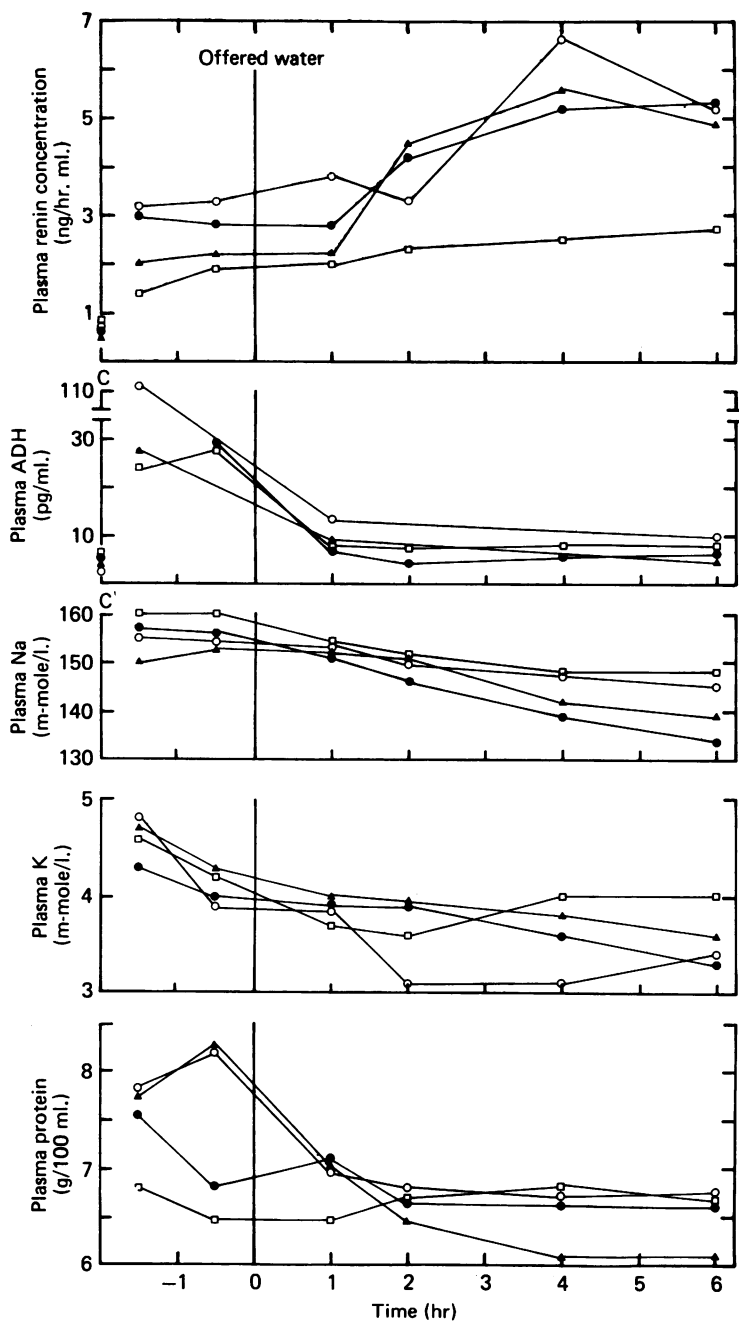


Fig. 1. Plasma parameters before and for 6 hr after rapidly drinking water. Sheep 47 (●), 86 (○), 95 (▲) and 532 (□). Water intake had been restricted to 250–750 ml./day for 8–15 days. C are control values obtained before water restriction.

Rehydration with water. Details of the volumes of water drunk by sheep 47, 86, 95 and 532 after a period of water restriction are shown in Table 1.

Changes in plasma renin concentration and plasma concentrations of ADH, Na, K and protein are shown in Fig. 1.

Renin concentrations after water restriction were 1.4–3.3 ng/hr.ml. compared with control values of 0.5–0.9 ng/hr.ml. The range was 2.7–5.3 ng/hr.ml. 6 hr after

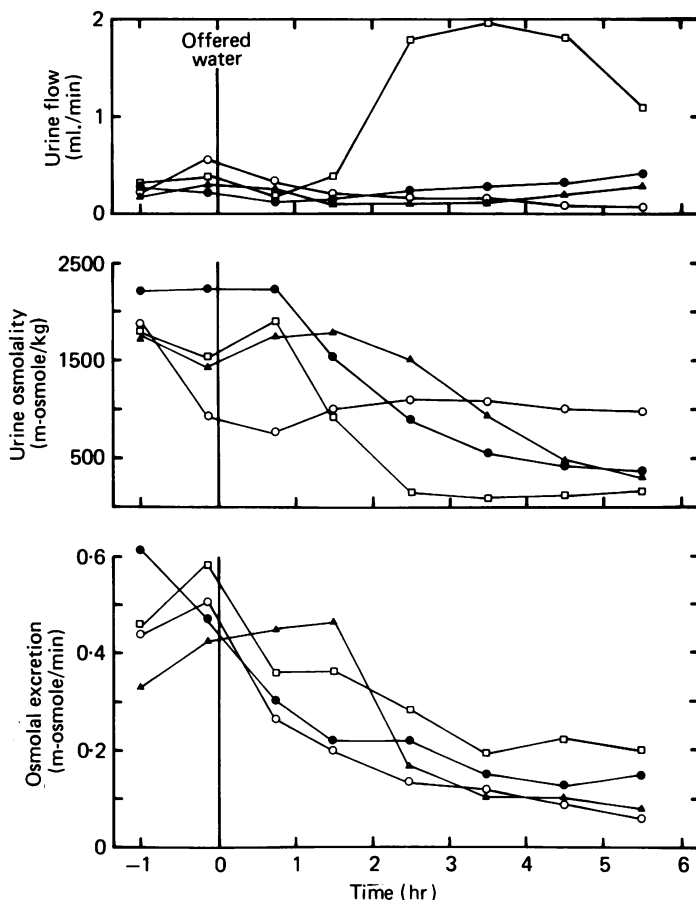


Fig. 2. Urinary parameters before and for 5.5 hr after rapidly drinking water. Sheep 47 (●), 86 (○), 95 (▲) and 532 (□). Water intake had been restricted to 250–750 ml./day for 8–15 days.

drinking, and the mean rose from 2.50 ± 0.32 to 4.55 ± 0.54 ng/hr. ml. ($P < 0.01$) confirming the results of earlier experiments (Blair-West *et al.* 1972). Plasma ADH concentrations were 2–7 pg/ml. in control samples and 24–111 pg/ml. at the end of water restriction. They fell to 7–13 pg/ml. 1 hr after drinking, and to 5–10 pg/ml. after 6 hr ($P < 0.001$). Plasma Na concentrations of the four animals were 150–160 m-mole/l. before drinking, and fell for 6 hr after drinking to 134–148 m-mole/l. Plasma K concentrations declined in all animals after drinking. K levels 6 hr after drinking were 0.4–0.9 m-mole/l. lower ($P < 0.01$) than the mean values of the samples

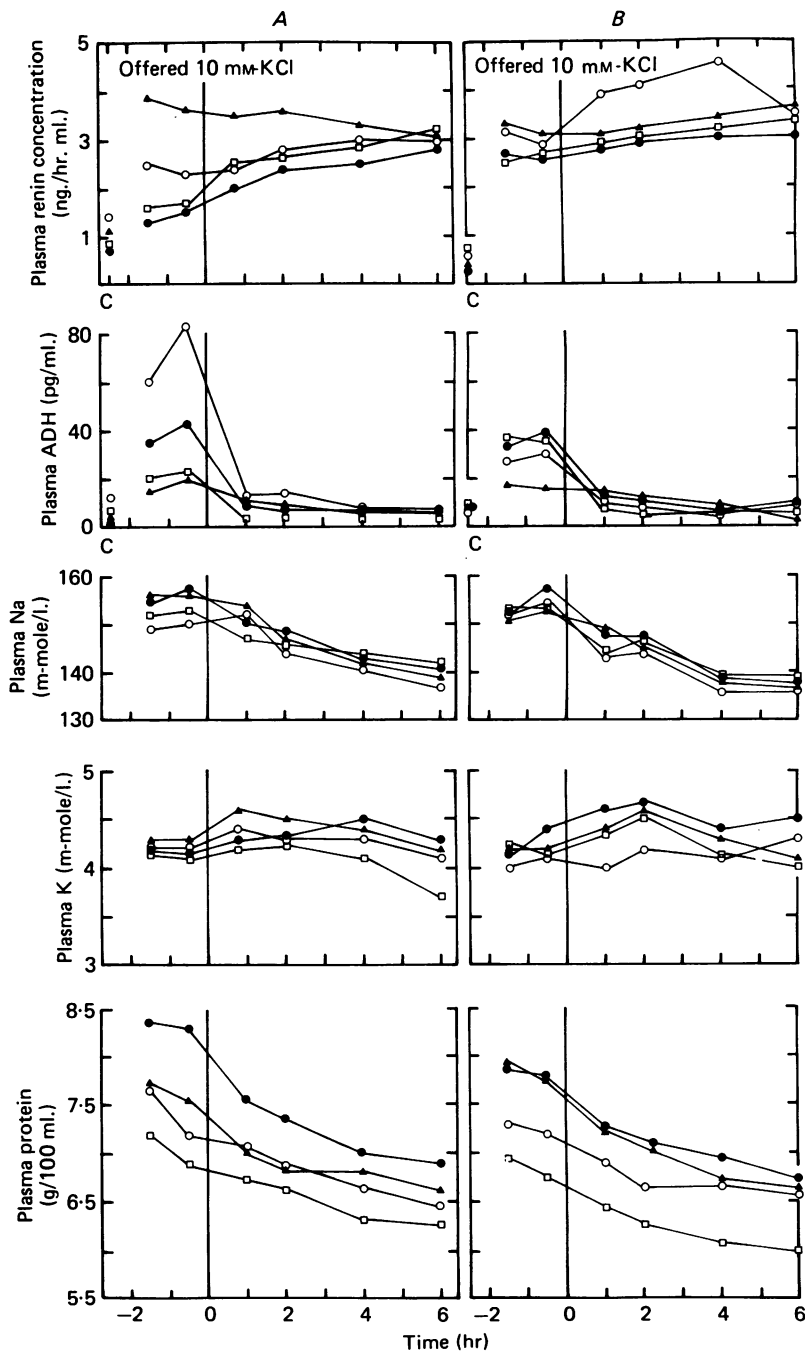


Fig. 3. *A*, left-hand side: plasma parameters before and for 6 hr after rapidly drinking 10 mM-KCl. *B*, right-hand side: as above, but additional KCl added to rumen over 80 min from 4.25 hr after drinking onwards: 50 m-mole to sheep 86 and 95; 100 m-mole to sheep 47 and 532. Sheep 47 (●), 86 (○), 95 (▲) and 532 (□). Water intake had been restricted to 250–750 ml./day for 8–15 days. *C* are control values obtained before water restriction.

collected before drinking. The effect of drinking on plasma protein concentrations varied from no change to a large fall.

The urinary changes following drinking are shown in Fig. 2. The urine flow rates

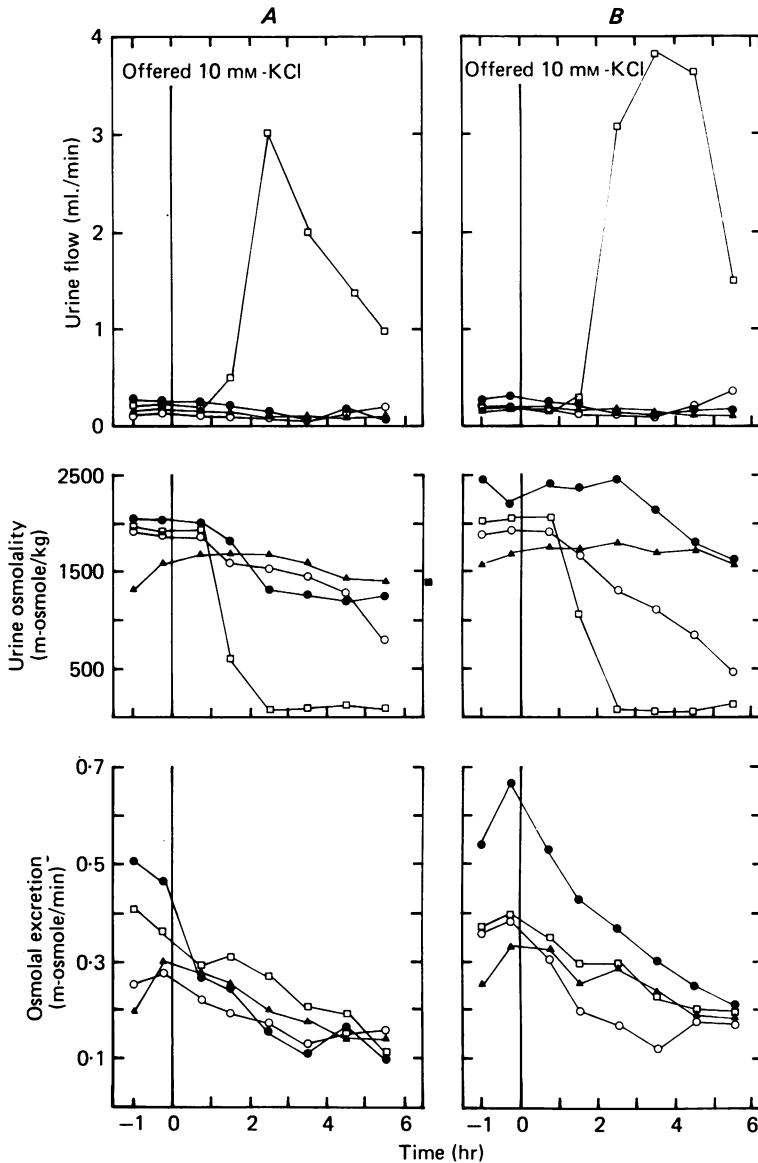


Fig. 4. *A* and *B*, urinary parameters before and after rapidly drinking 10 mM-KCl. Experimental details identical to those described in legend of Fig. 3.

of sheep 47, 86, and 95 remained as low (0.1–0.4 ml./min) during the 5.5 hr after drinking as they had been before the animals had drunk. Sheep 532 had a burst of diuresis which started 1.5 hr after drinking and diminished after the 4.5 hr collection. Urine osmolality fell considerably in three experiments but only the urine of sheep

532 became hypotonic to plasma. Osmolar excretion fell in all experiments, from 0.33–0.60 m-osmole/min pre-drinking, to 0.06–0.19 m-osmole/min, 5.5 hr later.

Rehydration with stabilization of plasma K concentration. Table 1 shows the volumes of 10 mM-KCl drunk and the amounts of K imbibed by the four sheep. In one set of four experiments, additional KCl (see Methods) was added to the rumen 4.25 hr

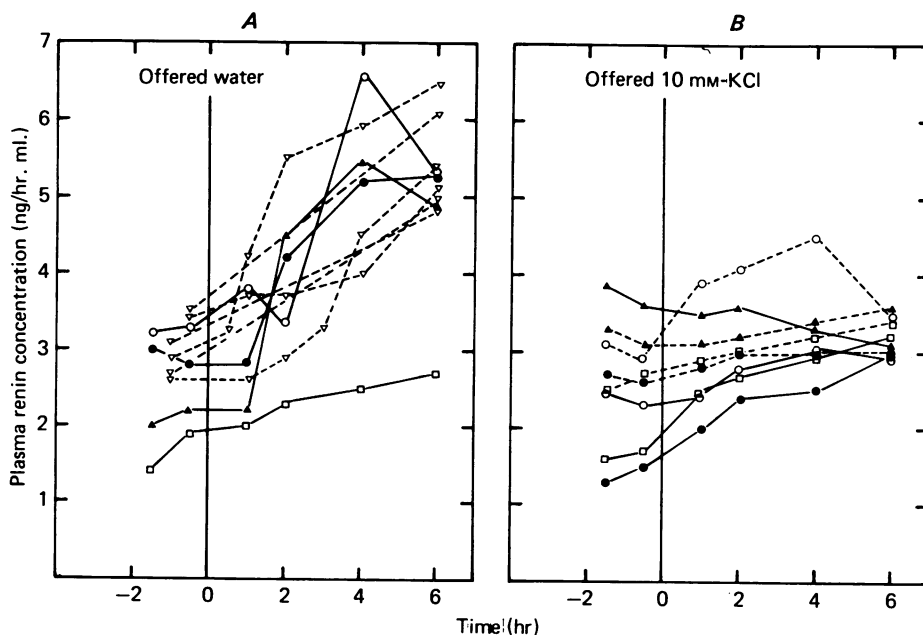


Fig. 5. *A*, left-hand side: plasma renin concentrations before and for 6 hr after rapidly drinking water. Values shown as (∇) are from earlier experiments (Blair-West *et al.*, 1972). *B*, right-hand side: renin concentration before and for 6 hr after rapidly drinking 10 mM-KCl with or without additional KCl added to rumen. Sheep 47 (●), 86 (○), 95 (▲) and 532 (□). Water intake had been restricted for 7–15 days.

after drinking to ensure that plasma [K] did not fall below pre-drinking levels. The results of the first four experiments are presented in Figs. 3*A* and 4*A*, and the results of the four experiments with late addition of KCl into the rumen are shown in Figs. 3*B* and 4*B*. The results in both procedures were very similar, and are therefore described together.

The effects on plasma renin, plasma ADH, Na, K and protein are shown in Fig. 3. Water restriction raised the renin concentration from 0.3–1.4 ng/hr.ml. to 1.4–3.8 ng/hr.ml. After the sheep drank KCl solution, the mean rose marginally over 6 hr from 2.6 ± 0.3 to 3.2 ± 0.1 ng/hr.ml. ($P = 0.05$).

Plasma ADH concentrations were 4–13 pg/ml. before water restriction and 16–83 pg/ml. at the end of water restriction. Within 1 hr of drinking, ADH levels had dropped to near control values. Mean plasma ADH concentrations before and 6 hr after drinking were 33 ± 6 and 7 ± 1 pg/ml. respectively ($P < 0.001$). Plasma Na concentrations fell steadily from 149–157 m-mole/l. pre-drinking to 136–142 m-mole/l. at the sixth hour.

Plasma K concentrations rose slightly in all experiments in the first 2 hr after

drinking and then dropped slightly in the next 4 hr in most experiments, so that the 6 hr values were similar to those before drinking. Mean values before and 6 hr after drinking were 4.21 ± 0.02 and 4.15 ± 0.08 respectively (difference not significant).

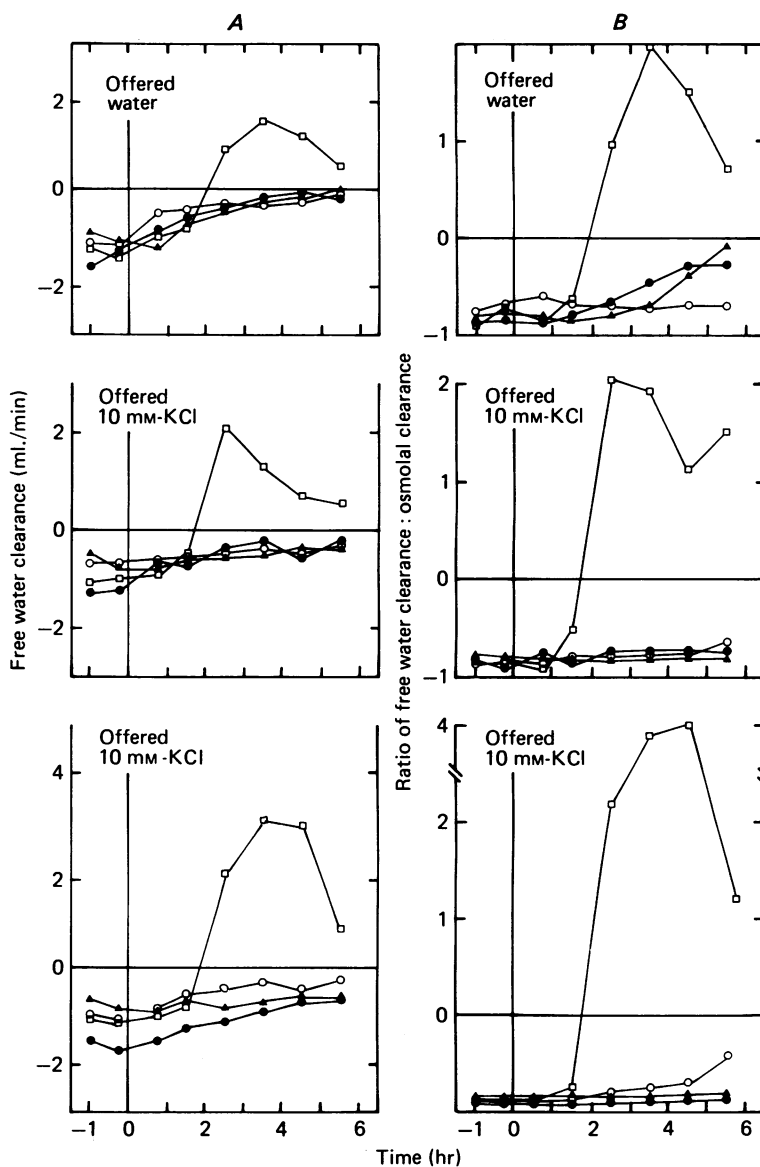


Fig. 6. *A*, left-hand side: free water clearance before and after rapidly drinking water (top panel), 10 mM-KCl (middle panel), and 10 mM-KCl with additional KCl added to rumen over 80 min from 4.25 hr after drinking (bottom panel). Sheep 47 (●), 86 (○), 95 (▲) and 532 (□). *B*, right-hand side: the ratio free water clearance : osmolal clearance in the same groupings as in *A* above.

Plasma protein concentrations decreased in all experiments in regular fashion after drinking. The pre-drinking levels were 6.7–8.4 g/100 ml. and those at 6 hr were 6.0–6.9 g/100 ml.

The urinary changes after drinking 10 mM-KCl are shown in Fig. 4. Urine flow rate remained low at 0.2 ml./min or less after drinking in six of the eight experiments, but sheep 532 had a diuresis in both experiments, similar to its response to drinking water (Fig. 2). Urine osmolality before drinking ranged from 1350 to 2450 m-osmole/kg and the effect of drinking varied from a small change (sheep 95) to a steep fall (sheep 532). Only the urine of sheep 532 became hypotonic to plasma. Osmolal excretion fell gradually after drinking in all experiments. Rates ranged from 0.20 to 0.66 m-osmole/min pre-drinking, and from 0.13 to 0.20 m-osmole/min after 5.5 hr.

Comparison of changes in plasma renin concentration. Previous experiments had shown that renin concentration rose after water-restricted sheep drank water *ad libitum* (Blair-West *et al.* 1972). Those results were combined with the results of the present water-drinking experiments (Fig. 5A) and then compared with the results of the experiments in which water-restricted sheep were given KCl in the drinking water and into the rumen in order to prevent a decline in plasma K concentration (Fig. 5B). Six hr after drinking water (ten experiments), mean renin concentration had risen 2.30 ng/hr.ml. ($t = 9.42$, $P < 0.001$). Six hr after drinking 10 mM-KCl (eight experiments), renin had risen 0.61 ng/hr.ml. ($t = 2.36$, $P = 0.05$, significance doubtful). There was no significant difference between pre-drinking renin concentrations in the two groups ('unpaired' $t = 0.72$, n.s.) but the difference 6 hr after drinking water or 10 mM-KCl was very highly significant ('unpaired' $t = 5.11$, $P < 0.001$).

Free water clearance. Plasma osmolality was not measured in these experiments therefore the value obtained by doubling plasma Na plus K concentrations was substituted for plasma osmolality in the calculations. (The correlation coefficient between $2 ([Na] + [K])$ and osmolality in sheep plasma was 0.90 (24 samples, range 278–313 m-osmole/kg). Variations as large as ± 10 m-osmole/kg in plasma osmolality had no substantial effect on calculated free water clearances.) Free water clearance, C_{H_2O} , varied from -0.47 to -1.76 ml./min after water restriction (Fig. 6A). Changes of C_{H_2O} after drinking water or 10 mM-KCl solution were similar. C_{H_2O} rose but remained negative for 5.5 hr except in sheep 532 in which C_{H_2O} was positive from the second to at least the sixth hour after drinking. The ratio, free water clearance:osmolal clearance, $C_{H_2O}:C_{Osm}$, was also calculated (Fig. 6B). Values varied from -0.66 to -0.87 before rehydration, remained stable for 5.5 hr after rehydration in most experiments, and negative in all experiments except those in sheep 532.

DISCUSSION

These experiments show that concentrations of both plasma renin and ADH increase in water-restricted sheep, but the nexus is broken after rehydration. Plasma ADH fell to control levels in less than 2 hr but renin rose even further. The rise of renin concentration after drinking was greatly attenuated when, instead of drinking water the animals drank 10 mM-KCl solution in order to stabilize plasma [K] close to pre-drinking values. The antidiuresis of dehydration persisted after rehydration in most experiments despite the fall of plasma ADH to control levels. C_{H_2O} and the ratio $C_{H_2O}:C_{Osm}$ remained negative, indicative of continuing ADH action.

The results of the four experiments with water drinking are consistent with earlier findings that plasma renin rises and remains high for at least 24 hr after water-

restricted sheep drink water (Blair-West *et al.* 1972). Observations in the present study were limited to 6 hr after rehydration because attention was directed to the events associated with the onset of the renin response. The present experiments suggest that the rise in renin after rehydration with water is due primarily to reduced plasma [K]. This effect is consistent with other findings (Veyrat, Brunner, Manning & Muller, 1967; Brunner, Baer, Sealey, Ledingham & Laragh, 1970; Davis, 1973) and demonstrates the important role of relatively small changes of plasma [K] in the control of renin release.

The present experiments also indicate that the rise in plasma renin after rehydration with water was not the result of diminished negative feed-back of plasma ADH on renin release because ADH fell rapidly in all experiments. However, one feature of the renin response to rehydration remains unexplained – that it did not fall to basal levels within 6 hr of rehydration despite prevention of the fall in plasma [K], and despite evidence of refilling of body fluid compartments in these and earlier experiments (Blair-West *et al.* 1972). This persistence of a high concentration of plasma renin indicates the continuing activity of another renin-releasing mechanism, possibly related to the virtual cessation of urinary excretion of Na and stimulation of the macula densa mechanism as proposed in earlier reports (Blair-West *et al.* 1972, 1977).

The speculation that the persistent antidiuresis after rehydration may have been due to continuing high levels of ADH caused by the high renin concentration (Blair-West *et al.* 1972, 1977) was not supported by plasma ADH measurements. In all experiments plasma ADH fell in the first hour after drinking to 7–16 pg/ml. while plasma Na concentration fell from 149–160 to 143–154 m-mole/l. with a mean fall of 4.7 ± 1.0 m-mole/l. ($P < 0.01$). Plasma ADH fell within 2 hr into the range of normally hydrated sheep. Therefore, the dehydration antidiuresis continued in the presence of normal ADH levels. Estimates of C_{H_2O} and $C_{H_2O}:C_{Osm}$ suggest continuing ADH activity for 6 hr after rehydration and earlier experiments (Blair-West *et al.* 1972) suggest that this activity may continue for at least 12 hr. Yesberg, Henderson & Budtz-Olsen (1970) showed that the relation of C_{H_2O} to C_{Osm} was a more reliable index of ADH secretion during fluctuations of C_{Osm} than the values of C_{H_2O} alone.

A similar renal response to rehydration was observed by McCance, Young & Black (1944) in human subjects who had been water-deprived for 84–108 hr. The urine volume during the first 24 hr after rehydration was slightly less than it had been during the last 24 hr of dehydration, irrespective of the dietary NaCl intake. They attributed this response to a reduction in the amount of salt presenting itself for excretion as indicated by reduced urinary excretion of chloride. They predicted that hormonal mechanisms would also be involved.

Robertson, Athar & Shelton (1977) and Robertson (1977) concluded that the ADH response normally evoked by changes in water status is due primarily to the associated changes in plasma osmolality and the system is reset by changes in blood volume. They showed that plasma ADH levels in man and rat fell close to zero as plasma osmolality declined below normal values. In the present experiments, plasma ADH levels did not fall to subnormal values as plasma Na concentration fell below the pre-dehydration range of 143–149 m-mole/l. Thus, plasma ADH levels 6 hr after

rehydration appear to be high in relation to the associated hyponatraemia and presumable hypo-osmolality of plasma evident in most experiments. The low urine flow rate, negative C_{H_2O} and negative $C_{H_2O}:C_{Osm}$ are quite consistent with above threshold levels of ADH. Furthermore, water-loading experiments in sheep indicate that plasma ADH levels may fall as low as 2.4 ± 0.4 pg/ml. (unpublished observations).

Possible explanations of these results are these. (i) The evidence that hypovolaemia causes a resetting of the osmoregulatory system so that the relation between plasma osmolality and plasma ADH concentration is shifted to the left (Robertson *et al.* 1977). Adjusting this reset relation back to normal may require more time than was allowed in these experiments, or expansion of blood volume after rehydration may not have been sufficient to achieve the normovolaemic set point. (ii) Some other mechanism supervened to maintain plasma ADH at normal levels despite hyponatraemia, e.g. the renin/angiotensin system. Increased blood angiotensin concentration may increase ADH secretion (Bonjour & Malvin, 1970; Malvin, 1971; Uhlich *et al.* 1975) although other studies indicate that this stimulus is at least partially dependent on an elevated plasma osmolality (Shimizu *et al.* 1973; Claybaugh, 1976). However, studies on the role of the renin/angiotensin system in ADH regulation have been concerned with whether administered renin or angiotensin stimulates ADH release rather than whether angiotensin may oppose the inhibition of ADH release by reduced plasma osmolality. In addition, the resetting of the osmoregulatory system described by Robertson *et al.* (1977) results in enhanced ADH levels at low plasma osmolalities in hypovolaemic states, and these are normally associated with increased activity of the renin-angiotensin system.

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